For the article: http://dx.doi.org/10.1038/jid.2008.178
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Why Rituximab Works

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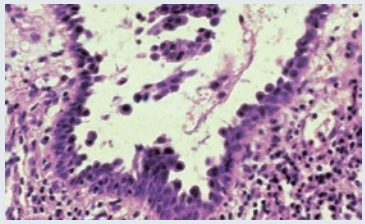

Pemphigus encompasses a group of autoimmune blistering diseases in which circulating immunoreactants—most notably IgG (particularly IgG1 and IgG4)—bind to the extracellular portions of desmosomal keratinocyte adhesion molecules (Sekiguchi *et al*., 2001) known as desmogleins and disrupt the adhesion between adjacent keratinocytes, producing intraepidermal blisters. In its idiopathic forms, pemphigus foliaceus (PF) and pemphigus vulgaris (PV), antibodies initially target desmogleins 1 (Dsg1) and 3 (Dsg3), respectively, leading to skin disease in patients with PF and skin and mucosal disease in patients with PV.

Recently, rituximab, a chimeric monoclonal antibody that targets the CD20 molecule, has been reported to benefit patients with PV (Joly *et al.*, 2007). CD20 is found exclusively on the surfaces of normal and neoplastic B cells. Rituximab is thought to act via a B-cell-depleting mechanism that includes complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and the induction of apoptosis (Johnson and Glennie, 2003). Thus, rituximab has been used in various B-cell-mediated malignancies such as B-cell non-Hodgkin's lymphoma (Cheson *et al*., 2002) and in autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and dermatomyositis (Leandro *et al*., 2002; Looney *et al*., 2005; Levine, 2005). Rituximab's benefit in patients with PV is thought to be due to the depletion of B cells that would otherwise give rise to pathogenic antibody–producing plasma cells.

In this issue of the Journal, Mouquet *et al.* studied 21 PV patients treated with rituximab and analyzed subsequent immunological changes, correlating them with clinical outcome. Total B-cell depletion was accompanied by significant decreases in IgM, but not IgG, levels. Over time, re-emergence of naive blood B lymphocytes occurred. Clinical responses were seen in patients who had decreased levels of anti-Dsg autoantibodies after treatment. Antimicrobial IgG levels did not change with rituximab treatment. The investigators also examined the VH-IgM and VH-IgG B-cell-receptor repertoire in two patients with PF and one with PV, both before and after rituximab treatment. In these patients, distortions of VH-IgM and VH-IgG were found before treatment but were not found after B-cell reconstitution following rituximab therapy. This suggests a mechanism by which rituximab may work and exhibit long-lasting effects: by initially depleting autoreactive B cells, leading to elimination of anti-Dsg autoantibodies. Eventually restoration occurs, but with naive (as opposed to primed) B lymphocytes with a diverse B-cell repertoire.

Through the following questions, we examine this paper in greater detail. For brief answers, please refer to http://network.nature.com/group/jidclub.

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QUESTIONS

1. What is the evidence for a mechanism of pemphigus pathogenesis, and which anti-desmoglein antibodies are responsible?
2. Why was rituximab considered a potential treatment for pemphigus?
3. Describe the methodological techniques employed in this study.
4. What were the findings of this study?
5. What may be the clinical implications of this article?

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